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CCN family member 1 (CCN1) is an early marker of infarct size and left ventricular dysfunction in STEMI patients

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ABSTRACT

Background and aims: CCN family member 1 (CCN1) has recently been proposed as a novel biomarker of myocardial injury, improving prediction of 30-day and one-year mortality following acute coronary syndromes. Among ST-elevation myocardial infarction (STEMI) patients, we evaluated the utility of CCN1 measured immediately before primary percutaneous coronary intervention (PPCI) as a predictor of two earlier endpoints: final myocardial infarct size and post-infarction left ventricular ejection fraction (LVEF). Furthermore, we evaluated the impact of CCN1 on the discriminatory power of the CADILLAC score.

Methods: STEMI patients were obtained from the SPUM-ACS cohort. Serum CCN1 was measured prior to PPCI. Linear regression assessed the association between CCN1, peak creatinine kinase (CK), and post-infarction LVEF. Cox models assessed an association between CCN1 and 30-day all-cause mortality.

Results: CCN1 was measured in 989 patients with a median value of 706.2 ng/l (IQR 434.3–1319.6). A significant correlation between CCN1, myocardial infarct size (peak CK) and LVEF was observed in univariate and multivariate analysis (both $p < 0.001$). Even among patients with normal classical cardiac biomarker levels at the time of PPCI, CCN1 correlated significantly with final infarct size. CCN1 significantly improved prediction of 30-day all-cause mortality by the CADILLAC score (C-index 0.864, likelihood-ratio chi-square test statistic 6.331, $p = 0.012$; IDI 0.026, $p = 0.050$).

Conclusions: Compared with classical cardiac biomarkers, CCN1 is potentially the earliest predictor of final myocardial infarct size and post-infarction LVEF. CCN1 improved the discriminatory capacity of the CADILLAC score suggesting a potential role in the very-early risk stratification of STEMI patients.

1. Introduction

CCN family member 1 (CCN1), also known as cysteine-rich angiogenic inducer 61 (Cyr61), is a cysteine-rich extracellular matrix protein secreted by endothelial cells, fibroblasts, smooth muscle cells and cardiomyocytes [1,2]. Its expression in cardiomyocytes is mediated by a host of stimuli including growth factors, angiotensin II, ischemia and tissue injury [3–5].

Amongst its numerous proposed functions, mounting evidence suggests an important role of CCN1 in vascular and myocardial injury. In the context of atherosclerosis, human atherosclerotic coronary and carotid arteries demonstrate an increased expression of CCN1 within the vessel connective tissue [4]. Furthermore, we have recently identified CCN1 as an early biomarker of myocardial injury enabling improved risk

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stratification among acute coronary syndrome patients [2]. Interestingly, soluble CCN1 was shown to be rapidly released following coronary artery occlusion, and even detectable prior to troponin, suggesting a role in the very initial stages of myocardial injury [2].

There is significant interest in the development of scoring systems that permit early risk stratification of patients following acute myocardial infarction (MI) [6,7]. Based on information only available at the time of PPCI, the CADILLAC score was shown to identify ST-segment elevation myocardial infarction (STEMI) patients at high risk of both short- and long-term mortality [6]. Furthermore, early risk stratification has been shown to permit the early identification of patients at low risk of complications who may benefit from early discharge [8]. Myocardial infarct size is a known predictor of poor short- and long-term outcomes following MI [9–13]. In the acute context, large infarctions have been shown to be associated with the development of cardiogenic shock, acute heart failure and ventricular arrhythmias [14–17]. In theory, the early detection of large infarctions could provide complementary information to currently available scoring systems, thus facilitating the early identification of patients at high risk of complications and optimising peri-PPCI care.

Given the early release of CCN1 following myocardial injury, we aimed to evaluate the utility of CCN1 as an early predictor of final myocardial infarct size as compared to other classical biomarkers in patients presenting with STEMI. Furthermore, we evaluated the potential improvement of risk stratification by the CADILLAC risk score with the addition of pre-PPCI CCN1.

2. Patients and methods

2.1. Patients

Data were obtained from the SPUM-ACS (Special Program University Medicine - Acute Coronary Syndromes) cohort of prospectively recruited patients admitted with ACS to four university hospitals in Switzerland. Further details of the SPUM-ACS cohort have been reported previously [18,19]. For the present study, the subgroup of patients hospitalised with STEMI between December 2009 and December 2012 who had blood drawn from the arterial sheath at coronary angiography prior to PPCI was selected (biomarker cohort). Blood was collected in serum tubes centrifuged, aliquoted, and stored at −80 °C.

2.2. Biomarker measurement and analysis

All biomarkers were measured in blood samples taken from the arterial sheath at the time of PPCI. Additionally, peak CK levels were measured 12–24 h later (highest recorded value before decline). As reported previously [2], concentrations of CCN1 were measured in duplicates of single serum aliquots blinded to the patient's data by means of numbered ID codes using a semi-automated solid phase enzyme-linked immunosorbent assay (EIA-5108, DRG Instruments GmbH, Marburg, Germany). Due to the absence of defined upper limit of normal of CCN1, the upper interquartile value reported in healthy controls was used for analyses where an upper limit of normal was required (56.2 ng/l) [20]. Troponin T was measured in serum aliquots using a high-sensitivity assay (hsTnT) using electrochemiluminescence immunoassays analysed on a cobas e 602 reader (all Roche Diagnostics, Mannheim, Germany) with assay characteristics as reported by the manufacturer. Due to the presence of missing values, 129 patients were excluded from analyses stratifying by baseline CK values, 248 patients were excluded from analyses stratifying by baseline CK-MB values, and 109 patients were excluded from analyses stratifying by baseline hsTnT values.

2.3. Myocardial infarct size

Myocardial infarct size was estimated using peak CK level as a surrogate marker. Due to the use of three different CK assays in this multicentre study, standardisation of CK values for comparison was achieved through use of the upper limit of normal of each assay. For the LVEF analysis, patients with previous MI were excluded from the analysis. LVEF was evaluated by ventriculography or by transthoracic echocardiography.

2.4. 30-day all-cause mortality

The incidence of events during follow-up was ascertained by telephone consultation 30 days post discharge [19]. When patients could not be reached for follow-up, medical information was obtained from primary care physicians, family members, hospital records or a registry office.

2.5. CADILLAC score

The CADILLAC score was calculated as previously reported [6]. Briefly, age >65 years [2 points], Killip class ≥2 [3 points], baseline left ventricular ejection fraction <40% [4 points], anemia [2 points], renal insufficiency [3 points], triple-vessel disease [2 points], and post-procedural Thrombolysis In Myocardial Infarction flow grade [2 points]).

2.6. Statistical analysis

Normally distributed, continuous variables are expressed as mean ± SD and compared using the 2-tailed Student *t*-test. Non-normally distributed continuous variables are expressed as a median with interquartile range and analysed using the Mann-Whitney *U* test. Comparisons between categorical variables were performed using the Pearson $\chi 2$ test. Univariate and multivariate linear regression was used to identify the association between CCN1 prior to PPCI as a continuous variable and: (i) symptom-to-catheter time, (ii) peak CK, and (iii) LVEF. To facilitate the graphical representation of comparisons between CCN1 and peak CK/LVEF, CCN1 values were divided into tertiles. Univariate and multivariate Cox proportional hazards models were used to evaluate the association between CCN1 level prior to PPCI and the primary endpoint. An optimal cut-off point for CCN1 was calculated using the Youden index. The discriminatory ability of the CADILLAC score with the addition of CCN1 and hsTnT was assessed using Harrell's concordance statistic (C-index), the likelihood ratio (LR) chi-square test and the integrated discrimination improvement (IDI) index. A *p*-value <0.05 was defined as statistically significant. Statistical analysis was performed using R version 3.5.1.

3. Results

3.1. Study population

Among 1029 patients admitted with a STEMI in the SPUM-ACS biomarker cohort, 40 (3.9%) patients were excluded from the analysis due to the absence of a peak CK value. The remaining 989 (96.1%) patients were included in the infarct size analysis. The derivation of the study population for each sub-analysis is shown in Supplementary Fig. 1. Comparison of the final study population with the non-biomarker SPUM-ACS STEMI cohort demonstrated only small differences in baseline characteristics (Supplementary Table 1).

3.2. Baseline clinical characteristics stratified by CCN1 level prior to PPCI

The median value of CCN1 was 706.2 ng/l (IQR 434.3–1319.6). When divided into tertiles 1 (T1), 2 (T2), and 3 (T3), this corresponded to CCN1 values of 371.6 ng/l (IQR 295.7–434.23 ng/l), 706.34 ng/l (604.4–836.5 ng/l), and 1740.9 ng/l (1323.1–2677.6 ng/l), respectively ($p < 0.001$). Compared with patients in T1, those in T2 and T3 were

significantly older (T1: 60.4 years, T2: 63.3 years, T3: 62.5 years, p= 0.012), more likely to be female (T1: 15.5%; T2: 19.7%; T3: 28.0%, p < 0.001), less likely to smoke (T1: 43.5%; T2: 49.7%; T3: 39.5%, p= 0.018), had a lower mean BMI (T1: 27.54 kg/m^2; T2: 26.84 kg/m^2; T3: 26.47 kg/m^2, p= 0.007), and a lower median eGFR (T1: 93.61 ml/min; T2: 92.22 ml/min; T3: 86.36 ml/min, p < 0.001) (Supplementary Table 2). Patients in T2 and T3 also exhibited higher-risk clinical features at the time of presentation, namely, a higher mean GRACE score (T1: 136.77; T2: 144.89; T3: 152.75, p < 0.001), a higher proportion of patients in Killip class 3/4 (T1: 1.2%; T2: 4.5%; T3: 11.2%, p < 0.001), and a lower median LVEF at the time of admission (T1: 50.0% (IQR 45.0%–60.0%); T2: 50.0% (IQR 42.0%–59.8%); T3: 45.5% (IQR 40.0%–55.0%, p < 0.001).

3.3. Correlation between CCN1 and symptom-to-catheter time

There was a significant negative correlation between symptom-to-catheter time and CCN1, with patients with the shortest symptom-to-catheter time having the highest CCN1 values prior to PPCI (T1: 4.42 h (IQR 2.69, 9.62), T2: 3.73 h (IQR 2.45, 6.98), T3: 3.13 h (2.13, 5.25), p < 0.001) (Supplementary Table 2). This correlation was confirmed with both univariate and multivariate linear regression controlling for age, sex, hypertension, diabetes, hypercholesterolemia, smoking, previous cardiovascular disease, GRACE score, Killip score, cardiac arrest at the time of presentation, and baseline eGFR (both p < 0.001). Stratification of symptom-to-catheter times by quintile, demonstrated that CCN1 was highest among patients undergoing PPCI within 2 h of symptom onset (Fig. 1A). Conversely, both CK and hsTnT demonstrated a significant positive correlation with symptom-to-catheter time (Fig. 1B and C).

3.4. Correlation between CCN1 and infarct size (peak CK and LVEF)

CCN1 prior to PPCI stratified into tertiles exhibited a significant positive correlation with peak CK, a surrogate marker for infarct size (Fig. 2A). This correlation was confirmed with CCN1 as a continuous variable in both univariate and multivariate linear regression controlling for symptom-to-catheter time as well age, sex, hypertension, diabetes, hypercholesterolemia, smoking, previous cardiovascular disease, GRACE score, Killip score, cardiac arrest at the time of presentation, baseline eGFR, hsTnT, and NT-proBNP (both p < 0.001) (Supplementary Table 3).

In a sub-analysis of 813 patients, after the exclusion of patients with a previous MI (n = 90) and those who did not undergo ventriculography (n = 86), CCN1 demonstrated a significant negative correlation with post-infarction LVEF as measured by ventriculography at the time of PPCI, with significantly reduced LVEF values with increasing CCN1 tertile (Fig. 2B). This correlation was significant in both univariate and multivariate analysis (CCN1 as a continuous variable) controlling for symptom-to-catheter time as well age, sex, hypertension, diabetes, hypercholesterolemia, smoking, previous cardiovascular disease, GRACE score, Killip score, cardiac arrest at the time of presentation, baseline eGFR, hsTnT, and NT-proBNP (both p < 0.001) (Supplementary Table 4).

In a subgroup of patients without previous MI, LVEF as measured by transthoracic echocardiography (TTE) was available (n = 274). The median time from PPCI to TTE was 2 days (IQR 1–3 days). CCN1 demonstrated a negative correlation with post-infarction LVEF as measured by TTE with a significant difference between T1 and T3 (Supplementary Fig. 2). This correlation was significant in both univariate and multivariate analysis (covariates as per Supplementary Fig. 4).

3.5. Correlation between CCN1 and infarct size after stratification by classical cardiac biomarker levels at the time of admission

Among 341 patients with normal CK values prior to PPCI, CCN1 tertile exhibited a significant positive correlation with peak CK values, a surrogate marker for infarct size (Fig. 3A). Among 187 patients with normal CK-MB values prior to PPCI, CCN1 tertile also exhibited a significant positive correlation with peak CK values (Fig. 3B). Among 42 patients with normal hsTnT levels prior to PPCI, there was a positive correlation between peak CK and CCN1 tertile with a significant difference found between CCN1 T3 with T1 (Fig. 3C).

3.6. CCN1 versus hsTnT in the early detection of myocardial injury

Of note, hsTnT also exhibited a significant positive correlation with both peak CK (Supplementary Table 3) and post-infarction LVEF (Supplementary Table 4) in multivariate analysis. Due to the absence of a defined upper limit of normal for CCN1, the upper quartile value of CCN1 previously reported among healthy individuals was used as a surrogate cut off [20]. Only three patients had CCN1 values below this cut off (median 27.68 ng/l).

An analysis of hsTnT tertiles exhibited a significant correlation with final infarct size (Supplementary Fig. 2A). However, among patients with normal CK values at the time of PPCI, hsTnT did not demonstrate a significant correlation with final infarct size (Supplementary Fig. 2B).

3.7. CCN1 and 30-day all-cause mortality: addition of CCN1 to the CADILLAC score

The all-cause mortality rate at 30 days was 2.4% (n = 24), with 58% (n = 14) of these deaths occurring in hospital. Univariate Cox regression

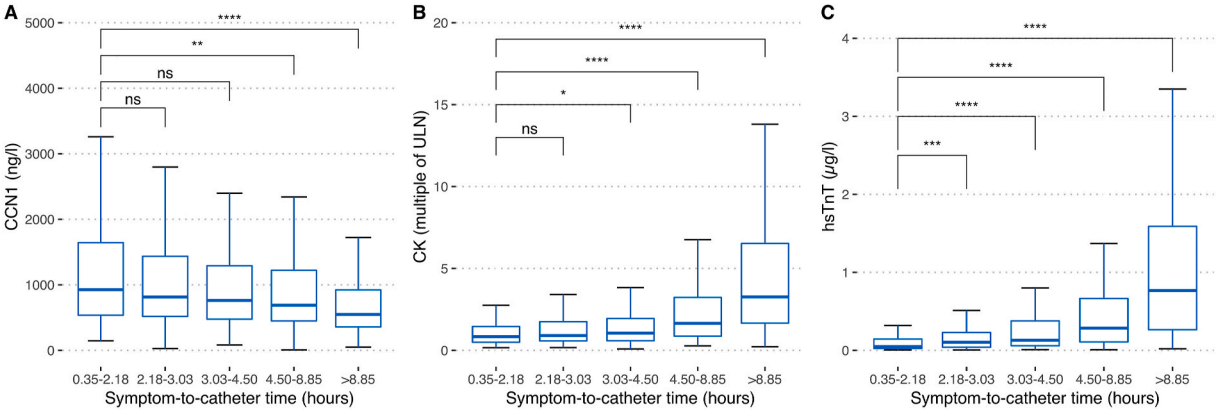

Fig. 1. Correlation between symptom-to-catheter time by quintile and biomarker levels at the time of PPCI.
(A) = CCN1; (B) = CK; (C) = hsTnT. p values derived using the Mann-Whitney U test. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$.

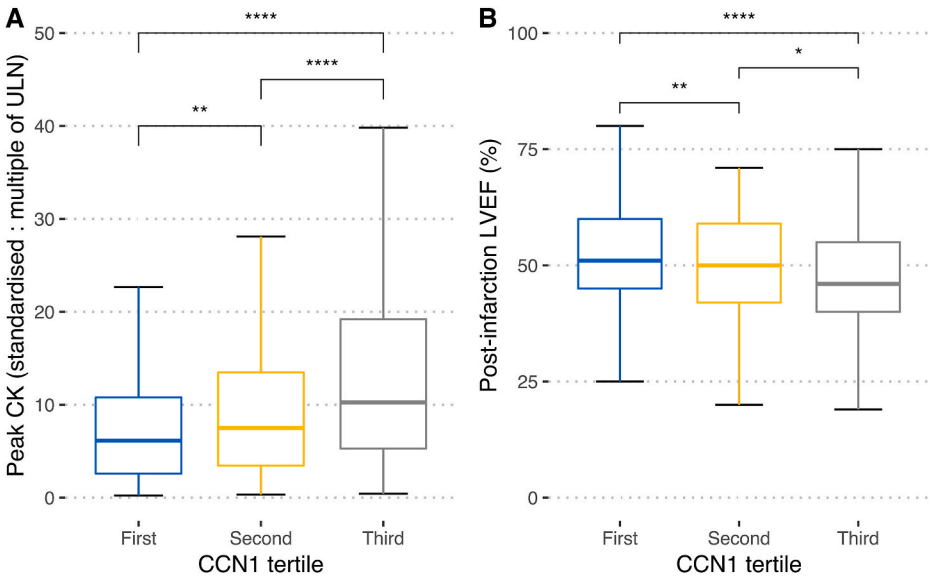

Fig. 2. Correlation between CCN1 prior to PPCI and (A) peak CK during the admission; (B) post-infarction LVEF as measured by ventriculography. *p* values derived using the Mann-Whitney *U* test. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$.

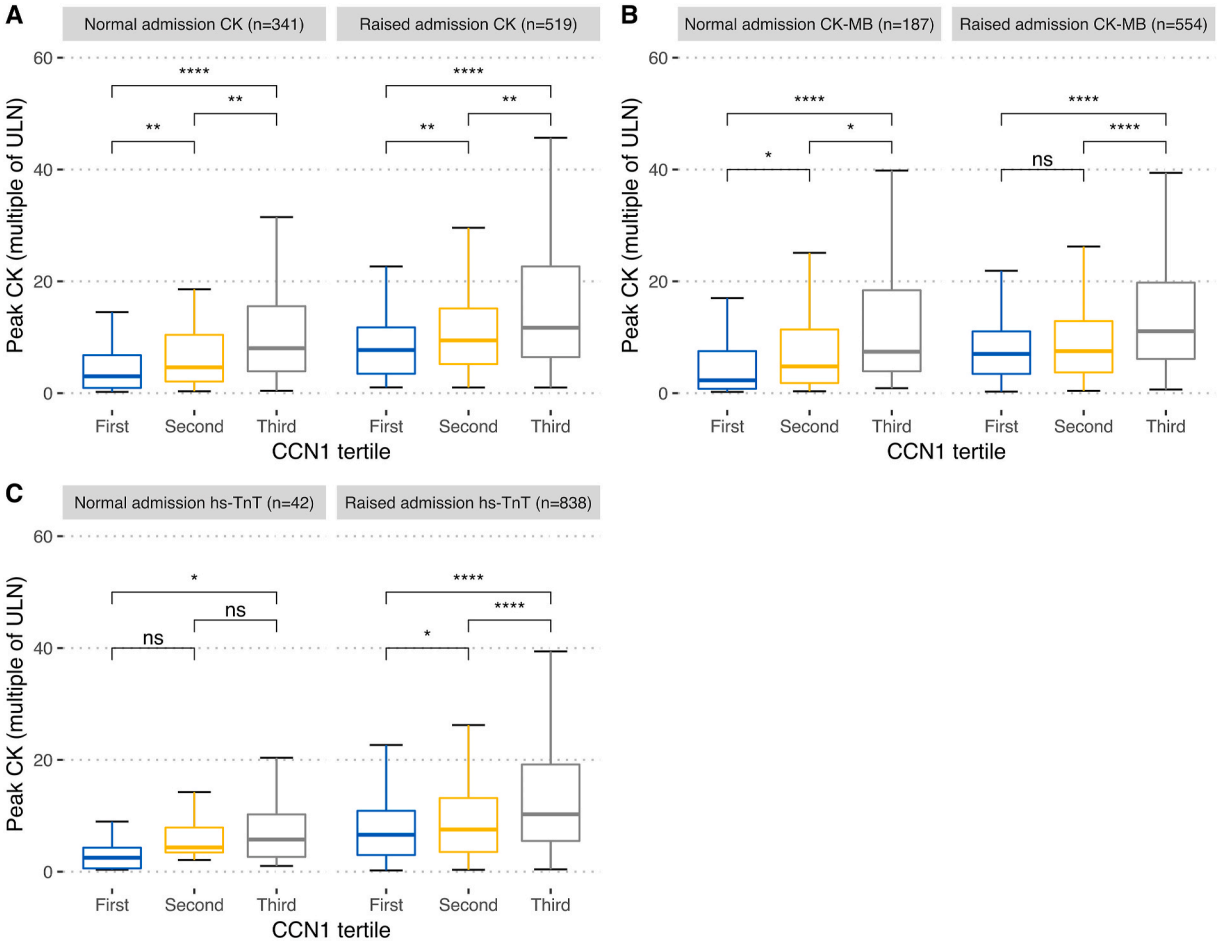

Fig. 3. Correlation between CCN1 prior to PPCI and peak CK level, stratified by classical cardiac enzyme levels prior to PPCI.
(A) Initial CK level; (B) initial CK-MB level; (C) initial hsTnT. Missing values: 129 patients excluded from analysis A due to missing baseline CK values; 248 patients excluded from analysis B due to missing baseline CK-MB values; 109 patients excluded from analysis C due to missing baseline hsTnT values. *p* values derived using the Mann-Whitney *U* test. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$.

demonstrated a significant association between CCN1 prior to PPCI and 30-day all-cause mortality, with a hazard ratio of 1.040 (95% CI 1.024–1.057, $p < 0.001$) for every 100 ng/l increase in CCN1. This association remained significant in multivariate analysis controlling for peak CK and post-infarction LVEF (HR 1.040, 95% 1.020–1.059, $p < 0.001$).

In univariate analysis, C-indices of CCN1 and the CADILLAC score were 0.676 (log-rank $p < 0.001$) and 0.840 (log-rank $p < 0.001$), respectively. Addition of CCN1 to the CADILLAC score resulted in an improvement in discriminatory performance (C-index 0.864, LR chi-square test statistic 6.331, p value 0.012; IDI 0.026, p value 0.050) (Fig. 4). The addition of hsTnT did not result in an improved discriminatory performance (C-index 0.843, LR chi-square test statistic 2.600, p value 0.107; IDI 0.017, p value 0.189). The addition of both CCN1 and hsTnT significantly improved the model (C-index 0.864; LR chi-square test statistic 11.089, p value 0.004; IDI 0.056, p value 0.020). The addition of CCN1 to a model of CADILLAC + hsTnT significantly improved discriminatory performance (C-index 0.864; LR chi-square test statistic 8.490, p value 0.004; IDI 0.038, p value 0.020). Using the Youden index, an optimal cut-off point for CCN1 of 1852 ng/l was calculated for the prediction of 30-day all-cause mortality. Kaplan-Meier analysis confirmed significant increased mortality among STEMI patient with pre-PPCI CCN1 values above this threshold (Fig. 5).

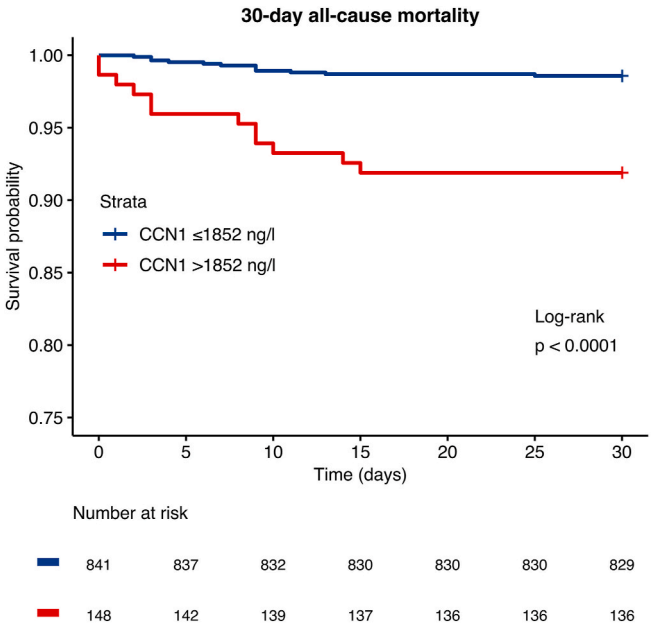

Fig. 5. Kaplan Meier survival analysis stratified by calculated CCN1 cut-off. An optimal CCN1 cut-off of 1852 ng/l was calculated using the Youden index. p value derived using the log rank test.

4. Discussion

The principal findings of this study are:

i. CCN1 measured immediately prior to PPCI exhibited significant correlations with peak CK, a surrogate marker of myocardial infarct size, and LVEF as measured by both ventriculography and TTE, with all correlations being independent of symptom-to-catheter time.

ii. Even among patients with normal classical cardiac biomarkers (CK, CK-MB, hsTnT) at the time of PPCI, CCN1 measured immediately prior to PPCI exhibited a significant positive correlation with final infarct size.

iii. Addition of CCN1 to the CADILLAC score resulted in a small but significant improvement in its discriminatory power.

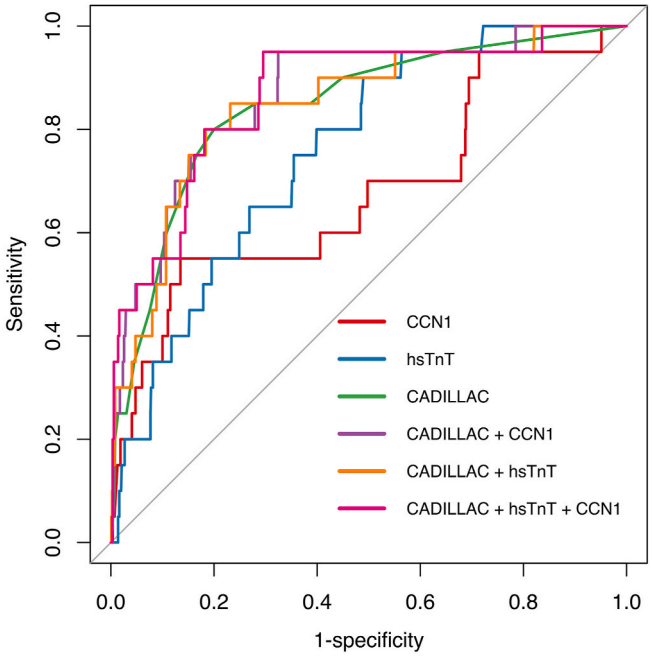

Fig. 4. Incremental discriminatory and reclassification capacities of CADILLAC score plus CCN1 and hsTnT.
C-index = concordance statistic; LR = likelihood ratio; IDI = relative integrated discrimination improvement. 109 patients without hsTnT values on admission were excluded from this analysis thus n = 880. p values for each Cox model determined using the log rank test. p values associated with LR and IDI used to determine whether discriminatory performance was significantly improved.

4.1. CCN1 as an early marker of myocardial infarction

Our results suggest a rapid increase of CCN1 following STEMI, with the highest values observed among patients undergoing testing within 2 h of symptom onset. Even among patients with normal classical cardiac markers at the time of PPCI, CCN1 was already significantly elevated and correlated with final infarct size. Interestingly, this was the case among the 42 patients (4.3% of the cohort) with normal hsTnT at the time of PPCI, a biomarker known to be exquisitely sensitive to myocardial damage.

In support of this finding is the rapid release of CCN1 seen in hypertrophic cardiomyopathy patients undergoing *trans*-coronary ablation of septal hypertrophy [2]. Furthermore, in a mouse model of ischemia-reperfusion, ligation of the left anterior descending artery was associated with a rapid increase in CCN1 mRNA expression when compared with controls [2]. CCN1 expression has also been shown to be elevated in cardiomyocytes following myocardial infarction [5]. These results suggest that CCN1 plays a role in the very initial stages of myocardial injury. This rapid response appears to be mediated by the role of CCN1 as an immediate-early gene, thus permitting its expression to be induced rapidly and transiently in a protein-synthesis independent fashion [21]. This provides a plausible mechanism for the early peak in CCN1 levels following infarction and why raised levels can be detected before other cardiac markers are raised.

CCN1 expression has been shown to be highly sensitive to a wide range of growth factors [22]. However, its expression is also sensitive to angiotensin II [4], hypoxia [23] and mechanical stretch [24], three factors that are theoretically perturbed in the early stages of myocardial infarction. Upon expression, the exact role of CCN1 is yet to be fully elucidated. However, CCN1 appears to exert numerous functions that may play a role in the pathophysiology of acute myocardial infarction.

CCN1 has been implicated in acute inflammation, with expression increased by inflammatory cytokines such as IL-1 and TNFα [25]. CCN1 has also been associated with fibroblast migration and monocyte adhesion [26,27], myocardial angiogenesis and remodelling of the vascular bed following myocardial injury [5].

Of note, only three patients (0.3% of the cohort) had normal CCN1 values at the time of PPCI, as defined by the upper IQR reported in healthy controls [20]. Interestingly, these patients had a mean symptom-to-catheter time of over 10 h, and thus a possible explanation of low levels in these patients was that CCN1 had returned to normal following an earlier peak value.

4.2. CCN1, prediction of infarct size, and risk stratification following STEMI patients

The possible role of CCN1 in acute inflammation and its rapid release kinetics provide a possible explanation for its significant correlation with post-infarction LVEF and infarct size. Post-infarction LVEF is a well-established risk factor for mortality following MI, particularly due to ventricular arythmias [13,28], although it has limitations as an isolated risk stratifier since the majority of MI patients maintain a preserved or only moderately reduced LVEF [29]. However, myocardial infarct size has important implications for patient outcomes. Infarct size has been shown to be significantly associated with mortality and MACE following hospital discharge [9–12]. Infarct size following STEMI is also associated with adverse myocardial remodelling and heart failure following hospital discharge [30]. In the acute setting, myocardial infarct size has also been associated with early cardiogenic shock and acute heart failure [14]. Additionally, infarct size has been strongly correlated with the risk of ventricular arrhythmias during the index admission [15,16]. Terkelsen *et al.* demonstrated that ventricular arrythmias, supraventricular arrythmias and conduction abnormalities were frequently seen in the 90 min following PPCI for STEMI. Furthermore, infarct size was shown to be significantly associated with sustained ventricular tachycardia and sinus bradycardia during this acute phase [17].

Given the importance of these acute complications of STEMI and their strong correlation with infarct size, the early prediction of large infarctions could provide significant benefits with regards to inpatient care. The early predictive power of CCN1 may provide an additional means of immediate risk stratification at the time of PPCI, enabling the optimisation of early inpatient surveillance and care immediately after PPCI.

4.3. CCN1 improves the discriminatory capacity of the CADILLAC score

Further support for the use of CCN1 in early risk stratification of STEMI patients is illustrated by its addition to the CADILLAC score, a score developed for the risk stratification of patients at the time of PPCI [6]. CCN1 has been shown to correlate significantly with all-cause mortality following myocardial infarction [2,31]. The present study demonstrates that the addition of CCN1 to the CADILLAC score results in a significant improvement in risk stratification. Despite hsTnT exhibiting a significant correlation with infarct size and LVEF, it did not significantly improve the discriminatory power of the CADILLAC score. This suggests that CCN1 could provide added value to the very early risk stratification of STEMI patients, although we recognise that the improved discriminatory performance is modest.

Interestingly, the present study demonstrates that this significant correlation between CCN1 and all-cause mortality is independent of infarct size (peak CK) and LVEF, suggesting that the association between CCN1 and MACE is more complex than simply that linked to myocardial infarct size. Further studies are needed to fully understand the roles of CCN1 following myocardial infarction.

4.4. Limitations

This analysis was based upon a single measurement of CCN1 at the time of PPCI. Inferences about the kinetics of CCN1 were made through comparisons of patients with differing symptom-to-catheter times. Although these inferences were corroborated by previously reported data [2], ideally patients would have had sequential CCN1 dosing at set intervals to fully define CCN1 release kinetics following STEMI. Additionally, CCN1 is not specific to the myocardium and thus it is possible that measured levels were not fully attributed to the myocardium. For example, CCN1 has been proposed as a potential ultra-early marker of acute kidney injury following renal ischemia [32]. However, given the context and the strong correlation with myocardial infarct size in this study, it is likely that the contribution of any non-cardiac source of CCN1 was insignificant. A further limitation was the use of peak CK as a surrogate marker of myocardial infarct size. Although this is a recognised method for estimating myocardial infarct size [33,34], an alternative method would have been through calculation of the area under the curve if numerous serum levels had been obtained at set intervals post-infarction. However, all biomarker-related predictors of myocardial infarct size remain indirect and liable to be influenced by other factors such as the reperfusion intervention itself which can affect peak levels and enzyme release kinetics. The optimal infarct size estimation method would have been through the use of cardiac imaging such as cardiac MRI or nuclear medicine imaging. Additionally, although ventriculography is a recognised method for the evaluation of LVEF, it is performed at the time of PPCI and is less precise than TTE. A subgroup analysis confirmed the correlation between CCN1 and TTE-derived LVEF, but ideally all patients would have had TTE-derived LVEF available. Finally, this study only considered STEMI patients and thus further work is needed to demonstrate its efficacy in NSTEMI patients, and also in other acute cardiac conditions such as heart failure and myocarditis.

4.5. Conclusion

Among STEMI patients undergoing PPCI, CCN1 measured immediately before PPCI was an early predictor of both final myocardial infarct size and post-infarction LVEF, and improved the discriminatory capacity of the CADILLAC score. These findings suggest a role for CCN1 in the very early risk stratification and management of STEMI patients.

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Author contributions

Study conception and design were undertaken by TM and SF. Data collection was undertaken by the SPUM consortium including RK, TL, CM, BG, DN, LR, DC, FM, NR and OM. Data analysis and interpretation of results was performed by TM, SF and OM. The manuscript was prepared by TM and SF. All authors reviewed the results and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.09.019.

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